Screening for reducing morbidity and mortality in malignant melanoma (Review)

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[Intervention Review]

Screening for reducing morbidity and mortality in malignant melanoma

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A B S T R A C T

Background

Screening for malignant melanoma has the potential to reduce morbidity and mortality from the disease through earlier detection, as prognosis is closely associated with the thickness of the lesion at the time of diagnosis. However, there are also potential harms from screening people without skin lesion concerns, such as overdiagnosis of lesions that would never have caused symptoms if they had remained undetected. Overdiagnosis results in harm through unnecessary treatment and the psychosocial consequences of being labelled with a cancer diagnosis. For any type of screening, the benefits must outweigh the harms. Screening for malignant melanoma is currently practised in many countries, and the incidence of the disease is rising sharply, while mortality remains largely unchanged.

Objectives

To assess the effects on morbidity and mortality of screening for malignant melanoma in the general population.

Search methods

We searched the following databases up to May 2018: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We also searched five trials registries, checked the reference lists of included and other relevant studies for further references to randomised controlled trials (RCTs), used citation tracking (Web of Science) for key articles, and asked trialists about additional studies and study reports.

Selection criteria

RCTs, including cluster-randomised trials, of screening for malignant melanoma compared with no screening, regardless of screening modality or setting, in any type of population and in any age group where people were not suspected of having malignant melanoma. We excluded studies in people with a genetic disposition for malignant melanoma (e.g. familial atypical mole and melanoma syndrome) and studies performed exclusively in people with previous melanomas.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The primary outcomes of this review were total mortality, overdiagnosis of malignant melanoma, and quality of life/psychosocial consequences.

Main results

We included two studies with 64,391 participants. The first study was a randomised trial of an intervention developed to increase the rate of performance of thorough skin self-examination. The intervention group received instructional materials, including cues and aids, a 14-minute instruction video, and a brief counselling session, and at three weeks a brief follow-up telephone call from a health educator, aimed at increasing performance of thorough skin self-examination. The control group received a diet intervention with similar follow-up. The trial included 1356 people, who were recruited from 11 primary care practices in the US between 2000 and 2001. Participant mean age was 53.2 years and 41.7% were men. This study did not report on any of our primary outcomes or the following secondary outcomes: mortality specific to malignant melanoma, false-positive rates (skin biopsies/excisions with benign outcome), or false-negative rates (malignant melanomas diagnosed between screening rounds and up to one year after the last round). All participants were asked to complete follow-up telephone interviews at 2, 6, and 12 months after randomisation.

The second study was a pilot study for a cluster-RCT of population-based screening for malignant melanoma in Australia. This pilot trial included 63,035 adults aged over 30 years. The three-year programme involved community education, an education and support component for medical practitioners, and the provision of free skin screening services. The mean age of people attending the skin screening clinics (which were held by primary care physicians in workplaces, community venues, and local hospitals, and included day and evening sessions) was 46.5 years, and 51.5% were men. The study included whole communities, targeting participants over 30 years of age, but information on age and gender of the whole study population was not reported. Study duration was three years (1998 to 2001), and outcomes were measured at the screening clinics during these three years. There was no further follow-up for any outcomes. The control group received no programme. The ensuing, planned cluster randomised trial in 560,000 adults was never carried out due to lack of funding. At the time of this review, there are no published or unpublished data on our prespecified outcomes available, and no results for mortality outcomes from the pilot study are to be expected.

The risk of bias in these studies was high for performance bias (blinding study personnel and participants) and high or unclear for detection bias (blinding of outcome assessment). Risk of bias in the other domains was either unclear or low. We were unable to assess the certainty of the evidence for our primary outcomes as planned due to lack of data.

Authors' conclusions

Adult general population screening for malignant melanoma is not supported or refuted by current evidence from RCTs. It therefore does not fulfil accepted criteria for implementation of population screening programmes. This review did not investigate the effects of screening people with a history of malignant melanoma or in people with a genetic disposition for malignant melanoma (e.g. familial atypical mole and melanoma syndrome). To determine the benefits and harms of screening for malignant melanoma, a rigorously conducted randomised trial is needed, which assesses overall mortality, overdiagnosis, psychosocial consequences, and resource use.

P L A I N   L A N G U A G E   S U M M A R Y

Screening for malignant melanoma (a type of skin cancer)

Review question

We reviewed the evidence about the effect of screening for malignant melanoma (a type of skin cancer) in people who were not suspected of having this cancer i.e. people with no suspicious mole or lesion (an area of skin with an unusual appearance in comparison with the surrounding skin), compared with no screening. We included any type of screening (e.g. skin self-examination, or by health professional) of any person not suspected of having malignant melanoma, irrelevant of age or gender. We included studies in people thought to have a high risk of developing malignant melanoma, but not those known to previously have had melanoma.

Background

Malignant melanoma is a skin tumour that can cause death by spreading to other parts of the body; the number of tumours is rising, while in many countries the risk of dying from the disease has not increased in a similar way. Screening for malignant melanoma is performed by visual self-examination of the skin, or visual inspection by a doctor or other health professional. Screening has the potential to reduce deaths from melanoma. However, there are also potential harms from screening people without symptoms of melanoma, such as finding melanomas that would never have caused symptoms if they had remained undetected (i.e. overdiagnosis), unnecessary surgery, and possible psychological stress. It is important to establish the evidence base for screening.

Study characteristics

Two studies met our inclusion criteria. The first study, based in the US, aimed to investigate how to increase the frequency people undertake skin self-examinations. All 1356 participants were asked to complete follow-up telephone interviews at 2, 6, and 12 months after randomisation. The average age of participants was 53.2 years; 41.7% were men.

The second study included 18 communities in Australia (63,035 adults) that were assigned to either have a three-year community-based melanoma screening programme or not. The study did not report information on the mean age or proportion of men and women in the whole study population, but the average age of those attending the skin screening clinics was 46.5 years and 51.5% were men. The study

lasted three years; outcomes were measured at the screening clinics during this time. There was no further follow-up. The purpose of the study was to investigate whether it was possible to conduct a larger trial, which was stopped by lack of funding.

The first study was funded by the National Cancer Institute (US); the second, by Queensland Cancer Fund and Queensland Health (Australia).

Key results

There was no information from either study on the effects of screening on total deaths, overdiagnosis from screening, or participant quality of life. The following outcomes were also not reported: deaths from skin cancer and false-positive/-negative rates (i.e. diagnosing a skin lesion as a melanoma when it is not present/not recognising a melanoma when it is present). Thus, we do not know whether screening for malignant melanoma results in any benefit, or whether such a possible benefit would be outweighed by harms of screening. General adult population screening for malignant melanoma is not supported or refuted by evidence from well-designed trials up to May 2018 and therefore does not fulfil accepted criteria for implementing screening programmes.

Reliability of the evidence

We could not assess the reliability of the evidence for our primary outcomes as they were not assessed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Screening compared with no screening for malignant melanoma

Screening compared with no screening for malignant melanoma

Patient or population: asymptomatic people

Settings: any setting

Intervention: screening

Comparison: no screening

Outcomes	Comments
Total mortality	Not measured
Overdiagnosis of malignant melanoma	Not measured
Quality of life/psychosocial consequences	Not measured
Mortality specific to malignant melanoma	Not measured
False positive rates	Not measured
False negative rates	Not measured

BACKGROUND

Description of the condition

The incidence of malignant melanoma in Western populations has risen many-fold over recent decades (Garbe 2009). This is likely due in part to an increase in exposure to risk factors, mainly ultraviolet (UV) radiation from the sun and artificial sources (Waldmann 2012). However, it is also clear that some of the rise in incidence is caused by overdiagnosis due to increased disease awareness and screening, since the large increases in incidence has not always been followed by similar increases in mortality (Norgaard 2011; Welch 2005). The prognosis of malignant melanoma is closely correlated to the thickness of the lesion at diagnosis, with thinner lesions having a much lower risk of metastases and a substantially better prognosis (Breslow 1970). The vast majority of the observed increase in the incidence of invasive malignant melanoma represents thin lesions (Norgaard 2011; Welch 2005), and the increase is even more pronounced for melanoma in situ (Johnson-Obaseki 2015). In contrast, the incidence of thick melanomas has remained largely constant in younger age groups, while some studies also suggest an increase of thick melanomas in older age groups (Norgaard 2011). The lifetime risk of dying from malignant melanoma in Western populations is strongly correlated with birth cohort, with an increasing risk in successive generations born from 1875 with a peak in cohorts born between 1936 and 1957 depending on region, followed by a gradually decreasing risk. This pattern suggests that mortality from malignant melanoma will gradually move to older age groups over time and eventually decrease, even without improved care or treatment (Autier 2015).

The risk of dying from malignant melanoma is higher in men than in women and is also correlated with skin complexion, with the highest risk in people with low skin pigmentation. In the US, the lifetime risk of dying from malignant melanoma is 0.24% among white women and 0.49% among white men, compared to 0.04% among black women and men (National Cancer Institute 2016). In Australia, malignant melanoma is substantially more common and mortality is also higher; the risk of dying from melanoma by the age of 85 years is 0.44% for women and 1.3% for men, and the risk of being diagnosed with melanoma is 4.3% for women and 7.1% for men (Cancer Australia 2016).

The most important avoidable risk factor is exposure to UV radiation from sunlight and artificial sources (Gandini 2005). Intermittent sun exposure confers an increased risk, while continuous exposure (i.e. from working outdoors) seems to be inversely associated with the risk of malignant melanoma (Gandini 2005). Exposure in childhood appears to induce a higher risk than exposure later in life (Gruber 2006). Observational studies found an association between artificial sources of UV radiation, such as solariums, and malignant melanoma (Lazovich 2016). Other risk factors include blonde or red hair, green or blue eyes, freckles, an inability to tan, a family history of malignant melanoma, and a large number of naevi and dysplastic naevi (Marks 2000). One randomised trial showed that sunscreen reduced the risk of malignant melanoma, but there were few events in the trial (Green 2011). Educational programmes, including counselling on the avoidance of intense and intermittent sun exposure and use of sunscreen, have been suggested as a way to reduce mortality from malignant melanoma through primary prevention; a Cochrane Review that evaluates this strategy is currently in progress (Langbecker 2014).

Screening for malignant melanoma is not recommended in the US (USPSTF 2016), Canada (CTFPHC 2013), Australia, or New Zealand (ACNMGRWP 2008). Germany has had a national screening programme for malignant melanoma since 2008 (Katalinic 2015), and opportunistic screening (i.e. when someone asks their doctor or health professional for screening, or screening is offered by a doctor or health professional outside of an organised screening programme) is increasingly used in many Western countries (Lakhani 2014). In Australia, the annual skin screening rate ranged from 10% to 50% of the adult population depending on how skin screening was defined (Balanda 1994; Borland 1995; Girgis 1991; Heywood 1994; Janda 2004), and the corresponding rate in the US was 14% to 20% (Federman 1997; Federman 2006; Ford 2004; Saraiya 2004). Several professional societies, who may have inherent vested interests, recommends skin screening. In Europe, a campaign involving dermatologists in over 30 countries (EUROMELANOMA) recommended "visiting your dermatologist regularly for a skin check-up" and conducting self-examination every month (EADO 2016). In the US, the American Cancer Society recommended a skin self-examination every month (American Cancer Society 2017) and the American Academy of Dermatology runs a skin screening programme wherein over 2.5 million skin screens have been conducted since 1985 (American Academy of Dermatology 2017).

Description of the intervention

Screening for malignant melanoma can be performed through visual self-examination of the skin or visual inspection by a general practitioner, dermatologist, or other health professional, which can be followed by dermatoscopy of identified lesions. Other methods to assist in diagnosing malignant melanomas are evolving and might also be used for screening, for example, teledermatology, mobile phone applications, and spectroscopy-based techniques (Dinnes 2015). The heightened sensitivity that these new methods might confer may increase both the major benefit (a mortality reduction) and the major harm (overdiagnosis) from the intervention. Among general practitioners, the sensitivity of visual inspection has been estimated to be 72% to 84% and specificity to be 70% to 71% (Brochez 2001). However, sensitivity and specificity do not take overdiagnosis into account; therefore, they are less informative in a screening context, where overdiagnosis is a higher concern than for diagnostic tests for symptomatic conditions. A suite of Cochrane Reviews are currently evaluating the accuracy of tests to assist in diagnosing malignant melanoma (Dinnes 2015).

Screening can be organised as programmes where all eligible people in a community are personally invited to screening or as public campaigns where the eligible population is encouraged to participate, for example, through the mass media or advertising.

How the intervention might work

Screening for malignant melanoma has the potential to reduce mortality from the disease through earlier detection, as prognosis is closely associated with the thickness of the lesion at the time of diagnosis. Screening might also result in less-invasive surgery and less use of adjuvant therapy if the incidence of late-stage disease is reduced (Welch 2011). For cancer screening to be effective, it must detect more cancers at an early stage and must lead to a lower incidence of late-stage disease over time (Keen 2015; Vainio 2002). If a decrease in late-stage disease does not occur, the increase

in early-stage disease may represent detection of lesions that are histologically malignant but would never have caused symptoms or death if they had remained undetected (i.e. overdiagnosis) (Biesheuvel 2007; Welch 2011).

Overdiagnosed malignant melanomas differ from false-positive findings in that they fulfil the histological criteria for malignancy (Welch 2011). It is not possible to know which specific individuals are overdiagnosed as practically all lesions are removed once they are diagnosed and treated and overdiagnosed individuals will therefore be considered as 'cured' (Biesheuvel 2007). The same is true for the mortality benefit (i.e. it is not possible to know which specific individuals who have avoided death from malignant melanoma due to screening as many fortunately survive also without screening due to treatment (Welch 2011). Overdiagnosis leads to overtreatment, which means that healthy people are exposed to unnecessary surgery and possibly adjuvant therapy. Overdiagnosis also constitutes unnecessary labelling of healthy people with a cancer diagnosis, which may result in psychological harm (Welch 2011). To evaluate the balance between benefits and harms of screening, it is important to consider both rare harms with major effects for few people and common harms with less-serious effects in many people (Harris 2014; UKNSC 2015).

As it is not always possible to distinguish between benign naevi and malignant melanomas with certainty through visual inspection or dermatoscopy alone, a number of unnecessary biopsies or local excisions of benign lesions will result from screening for malignant melanoma (i.e. false-positive findings) (Harris 2014; Welch 2005). This may lead to psychological stress in addition to the physical consequences of the excisions (Brodersen 2013). In contrast, malignant lesions may also be missed at screening (false negatives), which may lead to false reassurance and delayed contact with health professionals and thus delayed diagnosis and treatment (Goldenberg 2016). Screening for malignant melanoma may also lead to the discovery of other skin conditions, non-malignant as well as malignant, and result in treatment for these conditions. The consequences of this can be both beneficial and harmful.

Disease-specific mortality in cancer screening trials is an outcome prone to bias from misclassification of the cause of death (Gøtzsche 2013; Prasad 2016). Knowledge of the diagnosis increases the risk that the cause of death is falsely attributed to the disease in question although the true cause was another condition (termed sticky-diagnosis bias) (Black 2002). Conversely, a death can be falsely attributed to another cause, usually because some time has elapsed since diagnosis or because the connection is not always clear (termed slipper-linkage bias) (Black 2002). Total mortality is free from these and other biases and is therefore the most reliable outcome in cancer screening. The downside is that very large trials are needed to reliably detect a difference, as the effect of cancer screening is small in absolute numbers at the population level (Prasad 2016).

Why it is important to do this review

Screening for malignant melanoma is currently practised in many countries, apparently without support from randomised trials. This is problematic since data from randomised trials demonstrating that benefits outweigh harms is considered mandatory before the introduction of screening programmes for cancer (UKNSC 2015; WHO 2008). If screening for malignant melanoma can contribute to

reducing morbidity and mortality from this disease, it is important to clarify gaps in the evidence base so that this can be remedied. Screening for malignant melanoma may cause overdiagnosis of malignant melanomas and consequently overtreatment (Norgaard 2011). False-positive findings occur, which is known from breast cancer screening to cause substantial long-lasting psychological stress (Brodersen 2013). In addition, screening for malignant melanoma has a potential for opportunity costs.

A protocol for this review has been published (Johansson 2016).

OBJECTIVES

To assess the effects on morbidity and mortality of screening for malignant melanoma in the general population.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cluster-randomised trials, that compared screening for malignant melanoma with no screening, regardless of screening modality, type of population, or setting.

Types of participants

Any type of population and any age group that is not suspected of having malignant melanoma (i.e. asymptomatic people; those who do not present with a suspicious lesion). We included studies in high-risk populations such as older men and people with light skin living in countries with high sun exposure. However, we did not include studies in people with a genetic disposition for malignant melanoma (e.g. familial atypical mole and melanoma syndrome), neither did we include studies performed exclusively in participants with previous melanomas as we considered this control monitoring rather than screening and as the benefit/harm balance may differ substantially. However, we did include studies that did not explicitly exclude participants with previous melanomas.

As screening participants should not be invited based on a specific suspicion of malignant melanoma, we excluded studies of diagnostic tests or studies in symptomatic individuals who sought medical attention.

Types of interventions

Screening for malignant melanoma using any type of screening modality in any asymptomatic population and in any setting. We included studies that employed any screening frequency, including once-only. Screening could be performed by any type of health professional or through skin self-examination. The control intervention was no screening.

Types of outcome measures

Primary outcomes

1. Total mortality.
2. Overdiagnosis of malignant melanoma (i.e. excess number of malignant melanomas diagnosed in the screening group).

3. Quality of life (QoL)/psychosocial consequences (short-term: postintervention up to six months; medium-term: six to 12 months; and long-term: more than 12 months).

Secondary outcomes

1. Mortality specific to malignant melanoma.
2. False-positive rates (skin biopsies/excisions with benign outcome).
3. False-negative rates (malignant melanomas diagnosed between screening rounds and up to one year after the last round).
4. Use of surgery defined as more than local excision (included surgery with lymph node removal).
5. Use of surgery defined as local excision.
6. Use of adjuvant therapy.
7. Incidental findings of other skin conditions (benign or malignant).
8. Use of health services for any reason.

We included studies regardless of whether they quantified our prespecified outcomes or not. We planned to include at least all primary outcomes in our 'Summary of findings' tables.

We planned to quantify total and disease-specific mortality at five years, ten years, and for the longest follow-up period available.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 2 May 2018:

1. the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
2. the Cochrane Central Register of Controlled Trials (CENTRAL) 2018, Issue 3, in the Cochrane Library using the strategy in Appendix 2;
3. MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
4. Embase via Ovid (from 1974) using the strategy in Appendix 4; and
5. LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

Trials registers

We searched the following trials registers up to 21 May 2018 using the terms: melanoma, skin cancer, skin neoplasm, screening, early detection.

1. The ISRCTN registry (www.isrctn.com).
2. ClinicalTrials.gov (www.clinicaltrials.gov).
3. The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
4. The World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).
5. The EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from included studies

We checked the reference lists of included and relevant studies and reviews for further references to relevant trials. We used Web of Science for citation tracking of key articles.

Searching by contacting relevant individuals

We asked the lead authors of included studies if they were aware of any other published, unpublished, or ongoing studies, or results of studies, that would meet our inclusion criteria.

Adverse effects

We did not perform a separate search for adverse effects of the intervention. However, we searched for data in the included studies, but they did not report on adverse effects.

Data collection and analysis

Some parts of the Methods section of this review were similar to text in other Cochrane Reviews coauthored by KJJ and PCG, predominantly (Krogsbøll 2012).

Selection of studies

Two authors (MJ and KJJ) independently assessed the relevance of all titles and abstracts that were identified through the searches, and assessed full-text copies of potentially eligible articles. When necessary, the other authors (JB and PCG) resolved disagreements through discussion. Two authors (MJ and KJJ) independently searched reference lists, and one author (MJ) undertook citation tracking (Web of Science) of included articles.

We used Covidence to assess the titles and abstracts that were identified in our searches of the listed databases (Covidence), provided reasons for exclusions, and generated a flow chart. Covidence is an online systematic review platform provided by Veritas Health Innovation Ltd, an Australian not-for-profit company.

Data extraction and management

Two authors (MJ and KJJ) independently extracted data from the included trials and entered them into a data extraction form using Covidence (Covidence). One author (MJ) exported the extracted data into Review Manager 5 (Review Manager 2014). We planned to evaluate the data extraction form by pilot testing using a representative sample of studies; however, there was an insufficient number of included studies to be able to do this. When relevant information was missing from the reports, we contacted the study authors.

We extracted the following data from all included trials: study design, type of screening test used, total study duration, number of participants allocated to each arm, gender of participants, number lost to follow-up for each outcome, baseline comparability, setting, age, country, and date of study start.

We planned to extract the number of events or rates for total mortality, mortality specific to malignant melanoma, overdiagnosis, false positives, false negatives, surgical interventions defined as more than local excision, surgical interventions defined as local excision, and adjuvant therapy. For psychosocial consequences or QoL outcomes, we planned to

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extract the mean; standard deviation or standard error; and name, range, and direction of the scale used.

Assessment of risk of bias in included studies

We used Cochrane's 'Risk of bias' tool to formally assess the following domains, as described in Higgins 2011: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other biases, including the degree of contamination of the control group by searching for data on the rate of opportunistic screening in the control group.

We also planned to use the Outcome Reporting Bias in Trials (ORBIT) tool to assess outcome reporting bias (Kirkham 2010). We planned to assess the randomised groups for baseline comparability. We planned to use GRADE to assess the level of confidence in individual outcomes (Schünemann 2013).

Measures of treatment effect

For total mortality, mortality specific to malignant melanoma, overdiagnosis, false positives, false negatives, surgical interventions defined as more than local excision, surgical interventions defined as local excision, and adjuvant therapy, we planned to calculate the risk ratios (RR) and the risk differences (absolute risks). We planned to calculate standardised mean differences (SMD) for QoL outcomes if different scales were used and the scales were comparable. If the same scales were used in all studies, we planned to calculate the mean difference (MD). For all measures, we planned to calculate 95% confidence intervals (CI). We planned to define false positives as the rate of biopsies and local excisions with benign results in the intervention arm in the included trials.

Unit of analysis issues

For cluster-randomised trials, we planned to use effect estimates and standard errors from analyses that took clustering into account. When such estimates were not available, we planned to explore the possible effect of clustering in a sensitivity analysis.

Dealing with missing data

We planned to conduct analyses as intention-to-treat (ITT), when possible. We planned to contact authors if the reports did not contain sufficient data for this. If ITT analyses were not possible, we planned to undertake available-case analyses and assess the possible bias resulting from dropouts and losses to follow-up in best-case or worst-case analyses for all primary outcomes.

Assessment of heterogeneity

We planned to assess clinical and methodological differences between the trials before any meta-analyses were performed, and to judge whether we could pool trial results. We planned to explore statistical heterogeneity using the I^2 statistic. If we had found I^2 values above 30%, we planned to explore causes of heterogeneity in sensitivity analyses and subgroup analyses, and we planned not to present pooled results if we encountered unexplained heterogeneity that would render the pooled results uninformative.

Assessment of reporting biases

We intended to create funnel plots if more than 10 trials were found. Otherwise, we planned to narratively evaluate outcome reporting bias for individual outcomes in any of the included trials and explore this using the ORBIT tool (Kirkham 2010).

Data synthesis

If we had judged meta-analyses to be appropriate, we planned to use a random-effects model if there were substantial differences between the populations included; trial designs; and the type of, or frequency and number of, screens offered.

We planned to apply the trial sequential analysis model to the dichotomous outcomes (Brok 2008), but not to the continuous outcomes because the trial sequential analysis currently assumes MDs and not SMDs, which we expected was necessary to use. It is a statistical model, similar to interim analyses in clinical trials, used to quantify the reliability of data in cumulative meta-analyses, adjusting the P values for sparse data and multiplicity. The required information size (the number of participants required to accept or reject the hypothesis of a certain a priori anticipated effect) is calculated using the following five components.

1. Alpha = 0.05 (type 1 error).
2. Power = 0.90 (type 2 error 0.10).
3. Proportion (frequency) of participants experiencing serious adverse events and adverse events (based on observations).
4. Relative risk reduction (RRR) or increase of 20%.
5. Diversity (heterogeneity based on our observations).

Preferably, this model should be applied to trials with a low risk of bias only, but we planned to conduct analyses that also included trials with high risk of bias.

Where results were estimated for individual studies with low numbers of outcomes (fewer than 10 in total) or where the total sample size was fewer than 30 participants and an RR was used, we planned to report the proportion of outcomes in each group together with a P value from a Fisher's Exact test.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for the following groups:

1. light versus dark skin;
2. young versus old people;
3. women versus men;
4. high-risk versus low-risk countries;
5. screening by specialists (i.e. dermatologists or in screening units by specially trained staff) versus usual care (e.g. general practitioners); and
6. high-intensity versus low-intensity screening.

Sensitivity analysis

We planned to perform sensitivity analysis for studies with high versus low overall risk of bias concerning the randomisation process and blinded outcome assessment. If results differed between studies with high and low risk of bias, we planned to rely on studies with low risk of bias.

We planned to conduct a sensitivity analysis of any included studies that were prospectively registered in trials registers.

'Summary of findings' table

We included a 'Summary of findings' table in our review summarising our three primary outcomes and three of our secondary outcomes (mortality specific to malignant melanoma, false-positive rates, and false-negative rates). We planned to assess the certainty of the evidence using the five GRADE domains (risk of bias, inconsistency, imprecision, indirectness, and publication bias) (Higgins 2011; Schünemann 2013).

RESULTS

Description of studies

Results of the search

The searches of the five databases (see Electronic searches) retrieved 780 records. Our searches of other resources identified 17 additional studies that appeared to meet the inclusion criteria (14 identified through reviews of reference lists, two from citation-tracking, and one from a trials register). Therefore, we had a total of 797 records.

We excluded 775 records based on titles and abstracts. We obtained the full text of the remaining 22 records. We excluded 16 of these studies (see Characteristics of excluded studies table). We identified no ongoing studies and no studies are awaiting classification.

We included two studies reported in six publications. For a further description of our screening process, see the study flow diagram (Figure 1).

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Figure 1. Study flow diagram.


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Included studies

We included two studies. The first study was a randomised trial of an intervention developed to increase performance of thorough skin self-examination (TSSE), "the Check-It-Out Project" (Weinstock 2007). Study participants were recruited from 11 primary care practices in the US between 2000 and 2001. All participating primary care clinicians attended a workshop prior to initiation of recruitment in their clinics. The workshop focused on early detection of skin cancer. In total, 2126 people scheduled for a routine primary care visit were interviewed by telephone prior to that visit (i.e. the baseline interview). At the time of the visit, and after seeing the primary care clinician, a health educator randomised 1356 participants into either an intervention group (688 participants) or control group (668 participants). The mean age was 53.2 years, and 41.7% were men. The intervention group received educational materials, cues, aids, and a brief counselling intervention by a health educator aimed at increasing performance of TSSE for early detection of melanoma and other skin cancers. The educational materials advocated monthly TSSE with physician consultation for any new or changing skin lesions. The control

group received a diet intervention, which was intended to control for degree of contact with healthcare personnel. All participants were asked to complete follow-up telephone interviews at 2, 6, and 12 months after randomisation. The main outcome was rate of performance of TSSE. Rate of skin surgeries was retrieved from medical records for those participants who reported a procedure in follow-up telephone interviews.

The second study included was a cluster-randomised pilot study performed in Australia where nine communities including 35,058 adults who were 30 years or more were randomised to a three-year melanoma screening programme and nine communities served as controls, including 27,977 adults aged 30 years or more (Aitken 2002). The programme was implemented between 1998 and 2001. The purpose of the programme was to promote annual whole-body skin examination performed by medical practitioners, defined as visual examination of the skin, excluding areas covered by underwear, for early signs of skin cancer. The programme also encouraged regular whole-body skin self-examination and presentation of suspicious lesions to a doctor. The programme had three main components: 1. a community education component; 2. an education and support component for medical practitioners aiming to improve their skills in early diagnosis and management of skin cancer as well as to encourage doctors to offer skin screening to their patients; and 3. the provision of free skin screening services to which personal invitations for screening were posted to residents aged 30 years or more. Screening clinics were provided by primary care physicians and held in workplaces, community venues, and local hospitals and included day and evening sessions. The mean age of those attending the skin screening clinics was 46.5 years, and 51.5% were men; the study did not report the mean age or proportion of men/women in the whole study (communities) population. Outcomes from the screening clinics were measured between 1998 and 2001. There was no further follow-up for any outcomes. The originally planned outcomes were mortality from malignant melanoma in the inception cohort (i.e. all residents above 30 years of age) (primary outcome). Other outcomes included incidence of melanoma by tumour thickness, the impact of the intervention on the diagnosis and treatment of skin lesions, the proportion of the population undergoing skin screening, and cost outcome measures.

The plan was to expand the trial to include 44 communities (aggregate population of 560,000 adult men and women aged 30 years or more) (Aitken 2002), but due to lack of funding this trial was never initiated (Aitken 2017 [pers comm]).

Excluded studies

We excluded 16 publications after obtaining the full text following our review of titles and abstracts. None of these were randomised trials of the effects of screening for malignant melanoma on morbidity or mortality. The main reasons for exclusion was a non-randomised study design or an ineligible control group (e.g. studies where the control group received instructions for skin self-examination). The most relevant excluded study was the SCREEN (Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) study; an observational study comparing trends in melanoma mortality in regions with and without screening programmes in Germany (Breitbart 2012; Katalinic 2012). We describe this study in detail in the Discussion and Agreements and disagreements with other studies or reviews sections.

Risk of bias in included studies

Figure 2 and Figure 3 summarise the risk of bias of the two included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
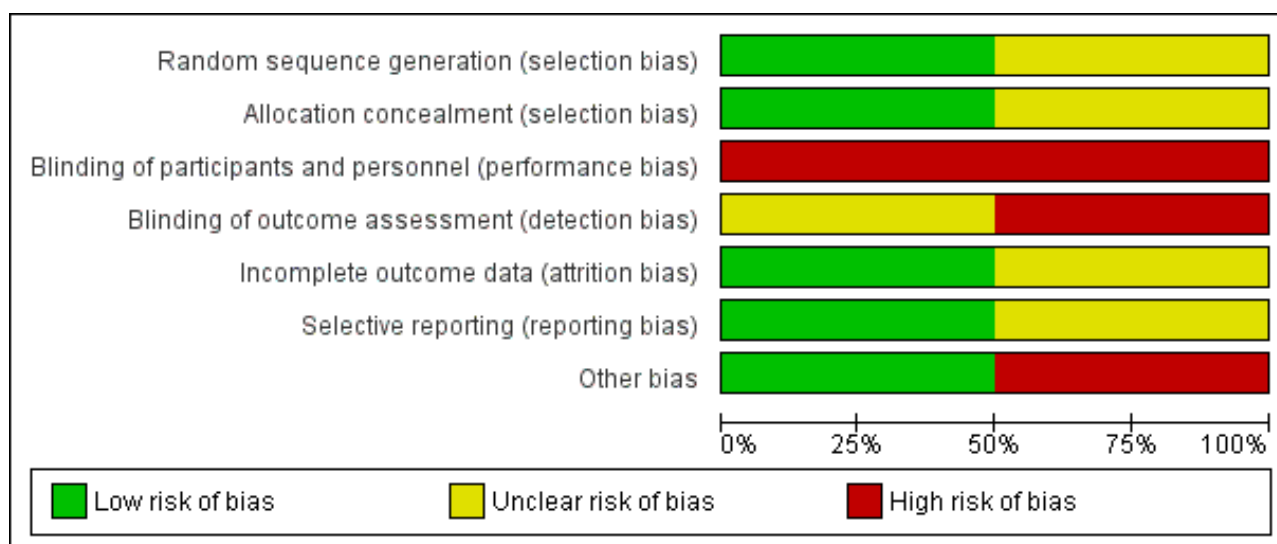
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

In "the Check-It-Out Project", randomisation was performed by participant selection of an opaque envelope with the assignment enclosed (Weinstock 2007). The risk of bias was low.

In the cluster randomised pilot study, randomisation of communities was within pairs (Aitken 2002). There was no information regarding sequence generation or allocation concealment. The risk of bias was unclear.

Blinding

In "the Check-It-Out Project", the interviewers who retrieved data on reported skin surgeries through telephone interviews with participants were not informed of the respondent's intervention assignment prior to any of these interviews (Weinstock 2007). However, intervention assignment could arguably have been revealed during the interviews. There was no information on whether the people who retrieved data on skin surgeries from medical records were blinded to intervention status. Blinding of participants was not possible due to the nature of the intervention.

The risk of performance bias would therefore be high and the risk of detection bias unclear.

In the cluster randomised pilot study, blinding of screening participants and healthcare personnel was not possible due to the nature of the intervention (Aitken 2002). Outcome assessment was planned to be registry based. We found no information on a plan for a blinded outcome assessment panel. The risk of bias would therefore be high, but no outcomes were reported.

Incomplete outcome data

In "the Check-It-Out Project", risk of attrition bias was low because there was a similar dropout rate across groups (Weinstock 2007). In the cluster randomised pilot study, no data on the prespecified outcomes of this review were reported; therefore, the risk of bias was unclear (Aitken 2002).

Selective reporting

In "the Check-It-Out Project", the risk of reporting bias was considered low because all preplanned outcomes were reported (Weinstock 2007). In the cluster randomised pilot study, no data on

the prespecified outcomes of this review were reported; therefore, the risk of bias unclear (Aitken 2002).

Other potential sources of bias

Weinstock 2007 was at low risk of bias because no other sources were identified. In the cluster randomised trial, the few clusters inferred another source of bias (Aitken 2002). Trials with few clusters are at high risk of bias because there are few units of randomisation. Thus, random error is likely and the risk of bias is therefore high.

Effects of interventions

See: **Summary of findings for the main comparison** Screening compared with no screening for malignant melanoma

There were some data from "the Check-It-Out Project" on the prespecified secondary outcomes of this review: 'use of surgery defined as local excision' and 'incidental finding of other skin conditions (benign or malignant)' (Weinstock 2007). However, this trial was not designed to answer our review question and the available data, therefore, had limited relevance when estimating the effect of screening on our prespecified outcomes. Due to the lack of data on indications for skin surgeries (i.e. suspicion of melanoma, or suspicion of other malignant or benign skin lesions), it was not possible to estimate the rate of false-positives based on the published data.

For the outcome 'incidental finding of other skin conditions (benign or malignant)', data were limited to few events; there were two severely atypical nevi (one in each group), seven squamous cell carcinoma (three in screening group, four in control group), and 10 basal cell carcinomas detected (seven in screening group, three in control group). Additionally, there were no data reported for benign skin conditions detected through screening.

There were 82 skin surgical procedures in the screening group and 46 in the control group over 12 months. Skin surgery was defined as "biopsy, cut or freeze", and there were no data on the proportion of either. Further, "skin surgeries were determined by examination of medical records of patients who reported a procedure". This may have introduced the risk of recall bias because people who have just received an intervention to increase skin self-examinations might have a higher probability of remembering going through skin surgery than people who have not received such interventions. We did not find it meaningful to estimate the effect of screening on "use of surgery defined as local excision" based on the published data. Finally, there were no malignant melanoma detected in the screening group and only one malignant melanoma detected in the control group. In conclusion, based on the data from this trial, it was not possible to assess our prespecified outcomes.

From the cluster randomised pilot study, there were no data with comparisons between the screening and control communities for the prespecified outcomes of this review (Aitken 2002), and none are to be expected (Aitken 2017 [pers comm]). This information was retrieved after contact with study authors. One publication presented data on the number of suspicious lesions and excisions performed in people screened at the screening clinics within the screening programme; in 15,343 people screened, there were 4129 suspected lesions and 14% of all screening examinations resulted in referral for at least one suspected lesion. Thirty-three histopathologically confirmed malignant melanomas were

diagnosed as well as one Hutchinson's melanotic freckle, which constituted 2% of all excised lesions. Due to the lack of data on rates of referral and diagnoses in the control arm and from screening examinations performed due to the screening programme but not at the screening clinics, and because 64% of those referred for suspected lesions after screening were already concerned about a specific skin lesion prior to the screening examination, it was not possible to estimate the rate of false positives based on the published data. The authors compared the percentage distribution according to thickness for the screen-detected melanomas to melanomas diagnosed in Queensland as a whole in the prescreening period from 1999 to 2002 and found a lower percentage of thick melanomas among the screen-detected cases. However, when a cancer screening programme may lead to the overdiagnosis of predominantly small invasive cancers and in situ lesions, such percentage distributions could be highly misleading and were, therefore, uninformative.

DISCUSSION

Summary of main results

We found no data from randomised trials to support or refute an effect of screening for malignant melanoma on morbidity or mortality (Summary of findings for the main comparison).

We identified one randomised trial of an intervention developed to increase the frequency of TSSE that met our inclusion criteria, but did not provide any data on our primary outcomes (total mortality, overdiagnosis of malignant melanoma, QoL/psychosocial consequences). The available data on our secondary outcomes were limited by few events and poor reporting. For our outcome Incidental finding of other skin conditions (benign or malignant), there were two severely atypical nevi (one in each group), seven squamous cell carcinoma (three in screening group, four in control group) and 10 basal cell carcinomas detected (seven in screening group, three in control group). Our key secondary outcomes (mortality specific to malignant melanoma, false-positive rates, false-negative rates) were not measured. It was not possible to estimate an effect of screening on any of our prespecified outcomes based on data from this trial.

Additionally, we identified one cluster-randomised pilot study for a larger, population-based cluster-randomised trial, but no results for our predefined outcomes were reported or were available in unpublished format, and the main trial was never initiated due to lack of funding (Aitken 2017 [pers comm]). In the pilot study, every seventh person screened had at least one suspicious lesion, while only one malignant melanoma was found for every 465 people screened and only 2% of all excised lesions constituted malignant melanomas. This indicated that many unnecessary biopsies were performed and substantial opportunity costs by screening for malignant melanoma both regarding health personal involved in the screening examinations and resources for histopathological investigation, which means economical resources were made unavailable to interventions with proven benefit.

Overall completeness and applicability of evidence

Despite extensive searches, we found no data from randomised trials on the primary outcomes of this review and very limited data on two secondary outcomes (from one trial). This review did not investigate the effects of screening people with a history of

malignant melanoma or in people with a genetic disposition for malignant melanoma (e.g. familial atypical mole and melanoma syndrome).

Quality of the evidence

Aitken 2002 was at high risk of bias for blinding and study design (cluster RCT) and unclear risk for the remaining domains. Weinstock 2007 was at high risk of performance bias and unclear risk for detection bias; the remaining domains were at low risk. We did not use GRADE to assess the quality of evidence because neither included study measured our primary outcomes or key secondary outcomes.

Potential biases in the review process

There were no data to assess.

We did not include non-randomised studies but we did report and discuss the result of some non-randomised studies that have had influence on screening policy in the Agreements and disagreements with other studies or reviews section. Since we did not perform a systematic search for non-randomised studies, this should not be viewed as a systematic or exhaustive summary of the evidence from non-randomised studies of the effects of screening for malignant melanoma.

We chose to include both studies of screening performed by a healthcare professional and skin self-examination because the mechanism of effect is similar (earlier detection). However, there may be differences regarding the magnitude of both benefit and harm depending on whether the screening is done by oneself or performed by a healthcare professional.

There are several methods to estimate overdiagnosis in cancer screening (Biesheuvel 2007). A more detailed description of these methods is outside the scope of this review, but randomised trials with long follow-up would be highly desirable to quantify this outcome.

Agreements and disagreements with other studies or reviews

The conclusions of this review are in accordance with recommendations from the US Preventive Services Task Force (USPSTF 2016), as well as official bodies in Canada (CTFPHC 2013), Australia and New Zealand (ACNMGRWP 2008), of which none recommend screening for malignant melanoma in the general population based on a lack of evidence for a beneficial effect of the intervention. The US Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults. Like the findings of our review, the US Preventive Services recommendation does not apply to people with familial atypical mole and melanoma syndrome, neither to people with previous melanoma.

Professional organisations, such as EUROMELANOMA (EADO 2016), the American Cancer Society (American Cancer Society 2017), and the American Academy of Dermatology (American Academy of Dermatology 2017), recommend skin screening, and some have argued for screening elderly, white men due to their increased risk of malignant melanoma (Coups 2010).

Evidence from non-randomised studies

An apparent effect of screening on melanoma mortality and on the rate of thick melanomas observed in non-randomised studies has been used in the argument for melanoma screening (Breitbart 2014; Curiel-Lewandrowski 2012; Geller 2015; McCleskey 2015; McFarland 2015; Robinson 2016a; Shellenberger 2016; Wainstein 2015). We did not search systematically for non-randomised studies and did not include them in our review. However, considering their potential and current impact, we decided to describe and comment on some of the most influential non-randomised studies.

The SCREEN study

The SCREEN study was the direct reason for implementation of melanoma screening in Germany, the world's only national, organised screening programme for malignant melanoma (Breitbart 2012; Katalinic 2012). The study, conducted in Schleswig-Holstein in Germany, compared trends for melanoma mortality and melanoma incidence before, during, and after the screening programme to trends in adjacent German and Danish regions with no screening programmes. The screening programme consisted of 1. an advertisement campaign (described in Breitbart 2012) aimed at the public to consult their doctor about primary and secondary preventive activities for skin cancer, and 2. eight-hour training courses where physicians were trained to actively inform and recruit people for skin cancer screening. The screening programme was gradually developed and implemented:

1. 2000 to 2001: a pilot project with courses for 200 physicians; 6000 people were screened;
2. 2001 to 2003: skin cancer awareness campaigns;
3. 2003: courses for 1673 (out of 2614) physicians with outpatient activities and 116 (out of 118) dermatologists in the region; and
4. 2003 to 2004: population-based once-only skin screening of 360,288 people.

The screening region had 2.8 million inhabitants, of whom 1.9 million met the eligibility criteria for screening within the programme (aged 20 years or more and being a policy holder of statutory health insurance (which applies to approximately 85% of the German population)). Physicians were paid approximately EUR 20 for every performed screen. Nineteen per cent of the eligible population were screened within the programme during the one-year main screening period (2003 to 2004). The male:female ratio for those screened was 1:3 (Breitbart 2012). The lowest participation rate was in people aged 70 years or more (12%). Fifty-two per cent of all melanomas diagnosed during the screening period were detected as part of the project. Data on the incidence of melanoma was extracted from the State Cancer Registry and data on mortality from melanoma was extracted from official mortality statistics. Analyses of incidence and mortality were based on the whole population (i.e. not only on the people screened).

The study showed that the age-standardised mortality rate of melanoma in the screening region decreased from 1.7 per 100,000 (95% CI 1.4 to 2.0) to 0.9 per 100,000 (95% CI 0.7 to 1.1), that is, a 48% reduction from the prescreening period (1998 to 1999) to five years postscreening (2008 to 2009), and almost equally in both sexes. In the adjacent regions and in the rest of Germany, the mortality rates from melanoma were stable.

We evaluated the risk of bias in the SCREEN study using the ROBINS-I tool (Risk Of Bias in Non-randomized Studies – of Interventions) (Sterne 2016). We found a low risk of bias with unpredictable direction in the following domains; 'bias in selection of participants into the study', 'bias in classification of interventions', and 'bias due to missing data'. We found a low risk of bias favouring controls in the domain 'bias due to deviations from intended interventions'. We found a moderate risk of bias with unpredictable direction for the domain 'bias due to confounding'. We found a serious risk of bias favouring the screened group for the domains 'bias in measurement of outcomes' and 'bias in selection of the reported results'. We judged the overall risk of bias to be serious and favouring screening. For further details, see the ROBINS-I form (Appendix 6).

In addition to the overall serious risk of bias, further data suggested that the validity of the results from the SCREEN study was questionable.

First, the five-year follow-up showed a decrease in melanoma mortality of almost 50% (Katalinic 2012), but after those five years, the mortality from melanoma increased rapidly in the screening region, and in 2012 to 2013 mortality rates were close to the rates observed before the SCREEN project and the same as those seen in the rest of Germany (Boniol 2015). Additionally, five years after the implementation of a nationwide skin screening programme in Germany, there was no beneficial effect (Katalinic 2015), as would be expected at this time based on the very large reduction seen in the SCREEN study. It has been argued that this disparity in outcomes was due to screening activities within the nationwide screening programme being less intensive than they were in the SCREEN study (Katalinic 2015). However, increases in melanoma incidence at the time of screening implementation were similar in the national screening programme (29% increase; Boniol 2015) and the SCREEN study (34% increase; Breitbart 2012). In addition, participation rates in the nationwide programme was reported as 31% in 2009 and 2010 (i.e. two years) (Boniol 2015), compared to 19% during one year in the SCREEN study. While the SCREEN study was a one-year project, the nationwide programme offers screening continuously which would also increase the chance of seeing a benefit. In conclusion, this indicates that the disparity in the mortality reduction seen in the SCREEN study and in the nationwide screening programme is unlikely to be explained by different intensity of screening and is more likely due to bias in the SCREEN study.

Second, in the SCREEN study, the participation rate was only 19% while the mortality reduction was almost 50%. This discrepancy could be explained by screening activities outside the programme, or a higher risk of melanoma death among people who attended screening compared to non-attendees. However, in the SCREEN project, 74% of people attending screening were women and participation rates were lowest in older age groups. Elderly men have the highest risk for mortality from melanoma, thus implying that the screening programme actually did not attract those people with the highest risk. Indeed, reductions in melanoma mortality were practically identical in men and women, despite only 10% of men participating compared to 27% of women. This raised a suspicion of systematic error rather than a true screening effect, especially as a 50% reduction based on 10% participation in men in itself seems highly unlikely, even accounting for strong self-selection bias.

Third, the decrease in melanoma mortality in the screening region started as early as 2002, that is, one to two years before the implementation of the main screening programme and only one to two years after the pilot project. Even if some of the mortality reduction would be attributable to the pilot project, it is still a remarkably prompt effect on population statistics given that only 6000 people participated in the pilot project out of an eligible population size of 1.9 million. Nothing similar has been seen in previous cancer screening programmes (Stang 2016a), and, considering the likely lead-time and time from a clinical diagnosis of melanoma to death from the disease, such a prompt effect on mortality seems biologically implausible.

Last, the reduction in mortality from malignant melanoma in the screening region was accompanied by a simultaneous substantial increase in deaths from malignant neoplasms of ill-defined, secondary and unspecified sites (Stang 2016b). Such trends were not observed in any of the adjacent regions. An incorrect counting of approximately 37 melanoma deaths per year in the screening region between 2007 and 2010 could explain the entire decline in melanoma mortality seen in the SCREEN study. The greatest reduction in melanoma mortality was seen in outpatient deaths, which are more prone to misclassification (Stang 2016b). It has been hypothesised that physicians practising in the screening region under-reported melanoma as a cause of death, as cause of death assessment was not blinded to screening status (Boniol 2015).

In conclusion, the transient decline in melanoma mortality observed in the SCREEN study was most likely not due to screening but differential misclassification of cause of death. Indeed, the available data from Germany indicated that organised screening did not affect mortality from malignant melanoma in a 5- to 10-year time frame, whereas it led to substantial increases in incidence, suggesting that overdiagnosis and overtreatment occurred. A longer follow-up without increased melanoma mortality would further support this conclusion.

Effect on rate of thick melanomas

Several non-randomised studies suggested a beneficial effect of screening through a decrease in the incidence of thick melanomas. For example, in one case-control study from Australia including over 3762 cases and 3824 controls, whole-body clinical skin examination in the three years before diagnosis was associated with a 14% lower risk of being diagnosed with a thick melanoma (greater than 0.75 mm) (odds ratio (OR) 0.86, 95% CI 0.75 to 0.98) (Aitken 2010). The reduction in risk of a diagnosis was greater for thicker melanomas: by 7% for melanomas 0.76 mm to 1.49 mm thick (OR 0.93, 95% CI 0.79 to 1.10; not statistically significant), by 17% for melanomas 1.50 mm to 2.99 mm thick (OR 0.83, 95% CI 0.65 to 1.05; not statistically significant), and by 40% for melanomas greater than 3 mm thick (OR 0.60, 95% CI 0.43 to 0.83). Screening was associated with a 38% higher risk of being diagnosed with a thin invasive melanoma (less than 0.75 mm) (OR 1.38, 95% CI 1.22 to 1.56) (Aitken 2010). In case-control studies using self-reported exposure, there is a risk of recall bias. In this case, recall bias would favour screening. However, it is less likely that recall bias would result in a gradient such as that seen for melanoma thickness. People who choose to participate in screening are often healthier and lead healthier lives (Raffle 2007). They are more likely to seek medical care and so their cancer is more likely to be detected earlier, even in the absence of screening (Raffle 2007). Therefore, screening

attendees also often have a better prognosis when diagnosed than other people due to differences in risk factors, socioeconomic status, and disease awareness. This phenomenon is called 'the healthy screenee effect' (Raffle 2007). In this case-control study, bias due to the healthy screenee effect may have explained the correlation between screening and melanoma thickness.

Although melanoma tumour thickness is the most important prognostic factor (Shaikh 2016), the rate of thick melanomas should be considered a surrogate outcome. This is because melanoma thickness is not a benefit in its own right but only relevant if translated into an effect on patient-relevant outcomes, such as less aggressive treatment over time or reduced morbidity or mortality from the disease (Hudis 2015). While melanoma tumour thickness is correlated with prognosis, we cannot be certain that earlier detection through screening will change prognosis. The correlation may be due to the biology of the individual tumour rather than causal.

AUTHORS' CONCLUSIONS

Implications for practice

Adult general population screening for malignant melanoma is not supported or refuted by current evidence from randomised controlled trials. The intervention therefore does not fulfil current criteria for implementation of population screening programmes (UKNSC 2015; WHO 2008).

We do not have sufficient evidence to determine the effects on morbidity and mortality of screening for malignant melanoma in the general population.

This review did not investigate the effects of screening people with a history of malignant melanoma or those who have a familial predisposition.

Implications for research

To determine the benefits and harms of screening for malignant melanoma, a rigorously conducted randomised trial is needed. As screening effects (both benefits and harms) are generally small at the population level, effects on total and disease-specific mortality are more likely to be created or erased by bias in a trial than what is commonly the case in trials of medical interventions. A trial would therefore have to be very large and rigorously conducted to allow an assessment of overall mortality, which is the only outcome that incorporates both the possible reduction of disease-specific mortality and the possible increased mortality arising from harmful effects of screening. Such a trial may not be feasible.

An alternative approach may be to conduct trials of, for example, old, light-skinned men or people with light skin living in countries with high sun exposure, because these selected population are at higher risk than other populations for developing melanoma.

Since opportunistic screening is already widespread in many countries, a challenge to any trial would be to make sure that the control group is not subject to such screening (i.e. to avoid contamination), since this may dilute both potential benefits and potential harms of screening picked up in the trial. Apart from a potential effect on mortality, as discussed above, other important outcomes to consider in future trials include overdiagnosis, psychosocial consequences, and resource use.

Future trials must ensure they follow the CONSORT guideline for clinical trials, to improve the quality of research, reducing risk of bias, and guide decision making (Moher 2010).

Before implementation of population-based screening for cancer in asymptomatic citizens, high-quality evidence from randomised trials showing that benefits outweigh harms is a specified requirement (UKNSC 2015; WHO 2008). The case of screening for malignant melanoma reinforces the importance of this requirement. First, as is apparent from the SCREEN study, non-randomised studies may lead to seriously misleading results. Second, screening has important harms, such as overdiagnosis and overtreatment of malignant melanomas, and robust trials would need to be performed to quantify them and weigh them against the benefit. Third, the majority of people who take part in the screening programmes cannot benefit from screening as they will never develop the disease. Fourth, screening programmes have a high potential for opportunity costs (Harris 2014). Fifth, when offering screening, healthcare systems invite asymptomatic people to an intervention that they have not asked for, which leads to ethical considerations that differ from those in regular health care (Sackett 2002).

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

C H A R A C T E R I S T I C S   O F   S T U D I E S

Characteristics of included studies *[ordered by study ID]*

Aitken 2002

Methods	Cluster randomised controlled study
Participants	Adults aged ≥ 30 years resident in intervention or control communities at the beginning of the intervention period and registered on the Queensland electoral roll.
	Sample size: intervention group: 35,058; control group: 27,977
Interventions	Community-based melanoma screening programme for 3 years vs no programme.

Aitken 2002 *(Continued)*

	Intervention group: community-based melanoma screening programme had 3 main components: 1. a community education component; 2. an education and support component for medical practitioners aiming to improve their skills in early diagnosis and management of skin cancer and to encourage doctors to offer skin screening to their patients; and 3. the provision of free skin screening services to which personal invitations for screening were posted to residents aged ≥ 30 years.

Control group: no programme. |
| Outcomes | Mortality from malignant melanoma, incidence of melanoma by tumour thickness |
| Notes | Funded by the Queensland Cancer Fund and Queensland Health (Australia) |

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information. Quote: "randomisation is within pairs."
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Registry-based outcome assessment, no blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No outcome reported.
Selective reporting (reporting bias)	Unclear risk	No outcome reported.
Other bias	High risk	Cluster randomised design with few clusters.

Weinstock 2007

Methods	Randomised controlled trial
Participants	People of both sexes attending a routine primary care visit in south-eastern New England, US.

Sample size: intervention group: 688; control group: 668. |
| Interventions | Instructional materials vs diet intervention

Intervention group: instructional materials (a booklet from the American Cancer Society on melanoma), including cues and aids (refrigerator magnet, hand mirror and body diagram to mark noted lesions); a 14-minute instruction video; a brief counselling session; and (at 3 weeks) a brief follow-up telephone call (from a health educator) and tailored feedback letters, aimed at increasing performance of thorough skin self-examination. |

Weinstock 2007 *(Continued)*

	Control group: received a diet intervention ("rate your plate") with similar follow-up.
Outcomes	Performance of thorough skin self-examination and rate of surgical procedures performed on the skin.
Notes	Funded by the National Cancer Institute (US).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by participant selection of an opaque envelope with the assignment enclosed." Comment: randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by participant selection of an opaque envelope with the assignment enclosed." Comment: randomisation method was adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Interviewers were not informed about allocation status and the same questionnaire was used for both groups. Data on skin surgeries from medical records were retrieved for participants who reported having a skin surgical procedure in a questionnaire only.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar dropout rate in the 2 groups (intervention vs control): 80% vs 80% at 2 months; 77% vs 73% at 6 months; and 67% vs 66% at 12 months.
Selective reporting (reporting bias)	Low risk	Likely reported preplanned outcomes (uptake, frequency of self-examination, number of lesions treated).
Other bias	Low risk	None identified

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Breitbart 2012	Non-randomised design.
Emmons 2011	Ineligible control; all groups got "educational brochures on the benefits of prevention and screening."
Geller 2006	Ineligible control; "Families in the usual care arm received the suggestion from the physician that patients diagnosed with melanoma notify the family members about their diagnosis and encourage the family members to be screened." Ineligible intervention; a mix of prevention strategies to result in "improvements in siblings' skin cancer risk reduction practices."

Study	Reason for exclusion
Girgis 1994	Ineligible control; the same intervention provided to control 1 month after the intervention group. Ineligible intervention; sun protection.
Greaney 2012	Ineligible control; all groups received "educational brochures on the benefits of prevention and screening."
Hiramoto 1986	Non-randomised design.
Katalinic 2012	Non-randomised design.
Oivanen 2008	Non-randomised design.
Rat 2012	Ineligible control; "In the control group, GPs [general practitioners] were asked to array a poster on melanoma prevention and information leaflets in their waiting room, and to carry out examination on their own initiative."
Rat 2014	Ineligible control; "In the control group, 10 general practitioners displayed a poster and the leaflets in their waiting room and examined patients' skin at their own discretion."
Robinson 2014	Ineligible control; intervention to promote skin self-examination.
Robinson 2016b	Ineligible population; people with previous melanoma.
Snow 1989	Non-randomised design.
Törnberg 1996	Ineligible control; letter with instructions for skin self-examination.
Walton 2014	Ineligible control; pamphlet with instructions for skin self-examination.
Youl 2005	Ineligible control; "This study sought to assess the impact of two methods of encouraging men to attend free open-access skin screening clinics."

A P P E N D I C E S

Appendix 1. Cochrane Skin Specialised Register (CRSW)

1 MESH DESCRIPTOR melanoma EXPLODE ALL AND INREGISTER
2 melanoma* AND INREGISTER
3 skin cancer* AND INREGISTER
4 skin neoplas* AND INREGISTER
5 MESH DESCRIPTOR Skin Neoplasms EXPLODE ALL AND INREGISTER
6 #1 OR #2 OR #3 OR #4 OR #5
7 MESH DESCRIPTOR Mass Screening EXPLODE ALL AND INREGISTER
8 screening AND INREGISTER
9 MESH DESCRIPTOR Early Detection of Cancer EXPLODE ALL AND INREGISTER
10 early detection AND INREGISTER
11 #7 OR #8 OR #9 OR #10
12 #6 AND #11

Appendix 2. CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Melanoma] explode all trees
#2 melanoma*:ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Skin] explode all trees

#5 (skin or epiderm* or derm* or cutaneous):ti,ab,kw
#6 #4 or #5
#7 #3 and #6
#8 malignant melanoma*:ti,ab,kw
#9 MeSH descriptor: [Skin Neoplasms] explode all trees
#10 skin cancer*:ti,ab,kw
#11 skin neoplas*:ti,ab,kw
#12 {or #7-#11}
#13 MeSH descriptor: [Mass Screening] explode all trees
#14 screening:ti,ab,kw
#15 MeSH descriptor: [Early Detection of Cancer] explode all trees
#16 Early detection:ti,ab,kw
#17 {or #13-#16}
#18 #12 and #17

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Melanoma/
2. melanoma$.ti,ab.
3. 1 or 2
4. exp Skin/
5. (skin or epiderm$ or derm$ or cutaneous).ti,ab.
6. 4 or 5
7. 3 and 6
8. malignant melanoma$.ti,ab.
9. exp Skin Neoplasms/
10. skin cancer$.ti,ab.
11. skin neoplas$.ti,ab.
12. or/7-11
13. Mass Screening/
14. screening.ti,ab.
15. "Early Detection of Cancer"/
16. Early detection.ti,ab.
17. or/13-16
18. 12 and 17
19. randomised controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized.ab.
22. placebo.ab.
23. clinical trials as topic.sh.
24. randomly.ab.
25. trial.ti.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. exp animals/ not humans.sh.
28. 26 not 27
29. 18 and 28

[Lines 19-28: Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. exp melanoma/
2. melanoma$.ti,ab.
3. 1 or 2
4. exp skin/
5. (skin or epiderm$ or derm$ or cutaneous).ti,ab.
6. 4 or 5
7. 3 and 6
8. malignant melanoma$.ti,ab.
9. exp skin cancer/
10. skin cancer$.ti,ab.
11. skin neoplas$.ti,ab.

Cochrane
Library

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Informed decisions.
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12. 7 or 8 or 9 or 10 or 11
13. exp mass screening/
14. screening.ti,ab.
15. exp early cancer diagnosis/
16. Early detection.ti,ab.
17. 13 or 14 or 15 or 16
18. 12 and 17
19. crossover procedure.sh.
20. double-blind procedure.sh.
21. single-blind procedure.sh.
22. (crossover$ or cross over$).tw.
23. placebo$.tw.
24. (doubl$ adj blind$).tw.
25. allocat$.tw.
26. trial.ti.
27. randomized controlled trial.sh.
28. random$.tw.
29. or/19-28
30. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
31. human/ or normal human/
32. 30 and 31
33. 30 not 32
34. 29 not 33
35. 18 and 34

Appendix 5. LILACS search strategy

((skin and (cancer$ or neoplas$ or melanoma$)) and (screening or "early detection"))

In LILACS we searched using the above terms and the Controlled clinical trials topic-specific query filter.

Appendix 6. ROBINS-I

Risk of bias assessment

N = no, PN = probably no, PY = probably yes, Y = yes

Signalling questions	Description	Response options
Bias due to confounding		
1.1. Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered.	The intervention and control regions could have different trends in melanoma mortality over time for reasons unrelated to screening. The study question was regarding the effect of "assignment to intervention" (once-only screening) (not "starting and adhering to intervention"). Outcomes were measured for the whole population, i.e. not only for those actually screened, which decrease the risk of self-selection bias and thus makes it more likely that the control and intervention groups are comparable.	PY
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:	—	—
1.2. Was the analysis based on splitting participants' follow-up time according to intervention received? **If N/PN:** answer questions relating to baseline confounding (1.4 to 1.6)	No; the outcome was assessed at the population level for both intervention and control areas.	N

(Continued)

If Y/PY: go to question 1.3.

1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN:** answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY:** answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	Not relevant.	—

Questions relating to baseline confounding only

1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Adjustments were made for age and sex. Baseline risk of mortality from malignant melanoma in the different regions before the intervention period was also taken into account.	PY
1.5. **If Y/PY to 1.4:** were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Yes; based on population registries.	Y
1.6. Did the authors control for any postintervention variables that could have been affected by the intervention?	No.	N

Questions relating to baseline and time-varying confounding

1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not relevant.	—
1.8. **If Y/PY to 1.7:** were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not relevant.	—
Risk of bias judgement	—	Moderate
Optional: what is the predicted direction of bias due to confounding?	—	Unpredictable

Bias in selection of participants into the study

2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	Unit of analysis was regions, and outcomes for the whole populations within each region were measured, thus there were no selection of	N

(Continued)

		individual persons into the study.	
2.2. **If Y/PY to 2.1:** were the postintervention variables that influenced selection likely to be associated with intervention?		—	—
2.3. **If Y/PY to 2.2:** were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?			
2.4. Do start of follow-up and start of intervention coincide for most participants?		Yes.	Y
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4:** were adjustment techniques used that are likely to correct for the presence of selection biases?		Not relevant.	—
Risk of bias judgement		—	Low
Optional: what is the predicted direction of bias due to selection of participants into the study?		—	Unpredictable

Bias in classification of interventions

3.1. Were intervention groups clearly defined?		Intervention group was defined by geographical region.	Y
3.2. Was the information used to define intervention groups recorded at the start of the intervention?		Yes.	Y
3.3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		No.	N
Risk of bias judgement		—	Low
Optional: what is the predicted direction of bias due to classification of interventions?		—	Unpredictable

Bias due to deviations from intended interventions

If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2

4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	This was a once-only screening intervention by visual inspection so deviations from usual clinical practise are judged unlikely. The screening programme also included public campaigns for secondary and primary prevention of skin cancer, but this is a question of external va-		PN

	lidity more than bias. The screening programme is not likely to have an effect on the care of patients with a diagnosed malignant melanoma to any significant extent. The screening programme was carried out in the intervention region and not in the control regions. There might have been some spill over effect, but probably not much.	
4.2. **If Y/PY to 4.1:** were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	Not relevant.	—
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important cointerventions balanced across intervention groups?	Not relevant.	—
4.4. Was the intervention implemented successfully for most participants?	Not relevant.	—
4.5. Did study participants adhere to the assigned intervention regimen?	Not relevant.	—
4.6. **If N/PN to 4.3, 4.4 or 4.5:** was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not relevant.	—
Risk of bias judgement	—	Low
Optional: what is the predicted direction of bias due to deviations from the intended interventions?	—	Towards the null

Bias due to missing data		
5.1. Were outcome data available for all, or nearly all, participants?	Outcomes were obtained from official mortality statistics, which were considered nearly complete. Emigration and immigration might have introduced some dilution of the screening effect.	PY
5.2. Were participants excluded due to missing data on intervention status?	No.	N
5.3. Were participants excluded due to missing data on other variables needed for the analysis?	No.	N
5.4. **If PN/N to 5.1, or Y/PY to 5.2 or 5.3:** are the proportion of participants and reasons for missing data similar across interventions?	Not relevant.	—
5.5. **If PN/N to 5.1, or Y/PY to 5.2 or 5.3:** is there evidence that results were robust to the presence of missing data?	Not relevant.	—

(Continued)

Risk of bias judgement	—	Low
Optional: what is the predicted direction of bias due to missing data?	—	Unpredictable

Bias in measurement of outcomes

6.1. Could the outcome measure have been influenced by knowledge of the intervention received?	Outcome assessors where the doctors that coded cause of death. These doctors were aware of intervention status. There were no blinded "cause of death" assessment committee. A high proportion of the doctors coding cause of death in the screening region took an active part in the screening programme.	Y
6.2. Were outcome assessors aware of the intervention received by study participants?	Yes, see above.	Y
6.3. Were the methods of outcome assessment comparable across intervention groups?	Probably yes.	PY
6.4. Were any systematic errors in measurement of the outcome related to intervention received?	Outcome assessors engaged in the screening programme might be more prone not to code malignant melanoma as cause of death.	PY
Risk of bias judgement	Serious	Serious
Optional: what is the predicted direction of bias due to measurement of outcomes?	—	Favours experimental

Bias in selection of the reported result

Is the reported effect estimate likely to be selected, on the basis of the results, from...	—	—
7.1. ... multiple outcome *measurements* within the outcome domain?	The starting point for the analysis coincided with a peak in mortality from malignant melanoma in the screening region and the stopping point for the analysis were the time of the lowest rate of mortality from malignant melanoma in the screening region, after which the rate starts to rise again. This choice of time points for the analysis yields the highest possible estimate of effect of screening on mortality from malignant melanoma and does not seem to be prespecified.	Y
7.2. ... multiple *analyses* of the intervention-outcome relationship?	Crude and age-adjusted standardised rates of death from malignant melanoma were analysed as well as annual percentage change between screening and control regions and for the pre- and postscreening period in the screening region.	PN
7.3 ... different *subgroups*?	Subgroup analyses were performed by sex and age groups.	PN

(Continued)

Risk of bias judgement	Serious		Serious
Optional: what is the predicted direction of bias due to selection of the reported result?	—		Favours experimental

Overall bias			
Risk of bias judgement			Serious
Optional: what is the overall predicted direction of bias for this outcome?			Favours experimental

WHAT'S NEW

Date	Event	Description
17 June 2019	Amended	Minor typo corrected
11 June 2019	Amended	The review was re-published to incorporate minor edits, which were made to improve clarification and readability.

CONTRIBUTIONS OF AUTHORS

MJ was the contact person with the editorial base.
MJ, KJJ co-ordinated contributions from the coauthors and wrote the final draft of the review.
MJ, KJJ drafted the clinical sections of the background and responded to the clinical comments of the referees.
MJ, KJJ worked on the methods sections.
MJ, KJJ responded to the methodology and statistics comments of the referees.
MJ, KJJ screened papers against eligibility criteria.
MJ, KJJ extracted data for the review and sought additional information about papers.
MJ obtained data on ongoing and unpublished studies.
MJ, KJJ appraised the quality of papers.
MJ, KJJ entered data into Review Manager 5.
MJ, KJJ analysed and interpreted data.
JB and PCG provided valuable comments and input for the protocol and review.
MJ is the guarantor of the update.

Disclaimer

DECLARATIONS OF INTEREST

MJ: none known.
JB: none known.
PCG: none known.

KJJ: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were unable to pilot test the data extraction form as planned because the search identified only two studies and they did not report data. We were unable to undertake the planned data syntheses, the funnel plots, the planned subgroup analyses, the planned sensitivity analyses, to produce a 'Summary of findings' table or to use GRADE assessment, because there were no primary outcome data, and there were limited data on two secondary outcomes (neither of which were included in the 'Summary of findings' tables).

In the protocol, we had not clearly expressed that our intention was to include studies of screening both by health professionals and through skin self-examination (we simply specified "any type of screening modality"). Therefore, we added a specific statement about inclusion of self-examination, under the Types of interventions section of this review to clarify that we also included studies on skin self-examination.

NOTES

The review was re-published to incorporate minor edits, which were made to improve clarification and readability.

INDEX TERMS

Medical Subject Headings (MeSH)

*Early Detection of Cancer; *Mass Screening [adverse effects] [methods]; *Self-Examination; Health Education; Medical Overuse; Melanoma [*diagnosis] [mortality] [prevention & control]; Pilot Projects; Quality of Life; Randomized Controlled Trials as Topic; Skin Neoplasms [*diagnosis] [mortality] [prevention & control]

MeSH check words

Adult; Female; Humans; Male; Middle Aged